Remarks

Status of the Claims and Support for the Amendments to the Claims

By the foregoing amendments, claim 1 is sought to be amended, and new claims 77-80 are sought to be added. Support for the amendment to claim 1, and for new claims 77-80, can be found throughout the specification. Specifically, support for the amendment to claim 1, and for new claim 77, can be found at page 21, lines 5-14. Support for new claims 78-80 can be found at pages 4-6, and throughout the Examples, specifically Examples 8-11. Therefore, these amendments introduce no new matter. Upon entry of the foregoing amendment, claims 1-4, 7, 8, 12, 69, 73 and 75-80 are pending in the application, with claims 1 and 73 being the independent claims.

Summary of the Office Action

In the Office Action dated July 26, 2007, the Examiner has made two rejections of the claims. Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

The Rejection Under 35 U.S.C. § 103(a) Over Chang, in View of Yu, Marks, Albritton, Wright and Morishige

In the Office Action at pages 2-6, section 5, the Examiner has rejected claims 1, 3, 7, 8, 12, 73, 75 and 76 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Chang, U.S. Patent No. 6,248,721 (hereinafter "Chang") in view of Yu *et al.*, *Oncogene 11*:1383-1388 (1995) (hereinafter "Yu"); Marks *et al.*, U.S. Published Patent Application No. 2001/0008759 (hereinafter "Marks"); Albritton *et al.*, U.S. Patent No. 6,448,390 (hereinafter "Albritton"); Wright and Huang, *Biochim. Biophys. Acta. 1103*:172-178 (1992)

(hereinafter "Wright"); and Morishige *et al.*, *Biochim. Biophys. Acta 1151*:59-68 (1993) (hereinafter "Morishige"). Applicants respectfully traverse this rejection.

The Examiner contends that Chang discloses that cationic liposomes, such as DOTAP/DOPE liposomes, can be ligand-targeted by covalently attaching ligands or antibodies to the surface of the cationic liposomes. Applicants respectfully disagree with the Examiner's contentions. The Examiner notes, however, that Chang does not disclose making the nucleic acid-cationic immunoliposome by directly conjugating an antibody fragment to the liposome within the ratio range recited in claim 1, followed by mixing the resulting cationic immunoliposome with nucleic acid. The Examiner relies on the disclosures of the remaining five cited references to cure the deficiencies in Chang.

With regard to Yu, the Examiner contends that this reference discloses cationic liposome-mediated E1A gene transfer, and the use of anti-p185 antibodies to construct immunoliposomes. The Examiner also contends that Yu discloses using a DNA:liposome ratio of 1:13, which allegedly falls within the range recited in claim 1, and that Yu discloses the addition of the antibody to the liposome, not the liposome:DNA complex. The Examiner also contends that Yu discloses that the cationic liposome consists of DC-cholesterol and DOPE at a ratio of 3:2. Applicants respectfully disagree with the Examiner's contentions.

The Examiner asserts that Marks discloses the use of scFv antibodies with a free cysteine reside at the C-terminus of the scFv for the preparation of targeted immunoliposomes. With regard to Albritton, the Examiner contends that this reference discloses cationic liposomes such as DOTAP/DOPC/DOPE containing an MPB-PE that can be directly conjugated to a sulfur atom which was part of a sulfhydryl group at the carboxy terminus of a protein. The Examiner further contends that Albritton discloses scFv

antibodies and their use in a chimeric protein as a delivery vehicle. Applicants respectfully disagree with the Examiner's contentions.

With regard to Wright, the Examiner contends that this reference discloses that an antibody can be attached to MPB-PE that has been used to stabilize the bilayer phase of DOPE liposomes in order to generate target sensitive immunoliposomes. Finally, the Examiner asserts that Morishige discloses conjugating Fab' fragments with liposomes containing MPB-PE at a ratio of 1 mg Fab' per 6 μmol of PC. The Examiner asserts that this ratio allegedly falls within the range recited in claim 1. Applicants respectfully disagree with the Examiner's assertions.

The Examiner asserts that it would have been obvious to combine the cited references in order to make a targeted cationic liposome containing a DNA therapeutic agent capable of targeting the immunoliposome to a Her2/neu expressing tumor. The Examiner contends that: 1) Chang discloses that cationic liposomes have been proven safe for inducing the transient expression of DNA in target cells, that antibodies or ligands can be covalently attached to the liposomes, and that DNA can be formed into a complex with the liposomes; 2) Yu discloses cationic liposome-mediated gene transfer and the attachment of an anti-Her2neu antibody to the liposomes; 3) Albritton discloses cationic liposomes comprising MPB-PE can be directly conjugated to thiolated proteins via a sulfur atom that was part of a sulfhydryl group; 4) Marks discloses anti-Her2/neu scFV antibody fragments conjugated to liposomes; 5) Morishige discloses a coupling ratio of antibody to liposome that allegedly falls within the ratios recited in the presently claimed invention; 6) the ordinarily skilled artisan is aware of the molecular weights of Fab' and scFv fragments; and 7) Wright discloses the attachment of antibodies to MPB-PE. The Examiner therefore concludes that it

would have been obvious for one of ordinary skill in the art at the time of filing to combine these references in the required manner. Applicants respectfully disagree with the Examiner's contentions and conclusions.

As set forth in *Graham v. John Deere Co. of Kansas City*, "[u]nder § 103, the scope and content of the prior art to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined." 383 U.S. 1, 17 (1966). Applicants respectfully submit that the differences between the presently claimed invention and the references cited by the Examiner are so great that it would not have been obvious to combine the various citations, as required by the Examiner, in order to render the presently claimed invention obvious.

Throughout the present Office Action, the Examiner asserts that Applicants are arguing the cited references separately (*see, e.g.,* Office Action at page 6). Applicants respectfully disagree with the Examiner and contend that the cited references are not being attacked individually as discussed in M.P.E.P. § 2145(IV), but rather, are addressing the deficiencies of the entire *prima facie* case of obviousness together. The discussion of each reference in order is only done so as to facilitate discussion, in a logical fashion, of the six references cited by the Examiner.

Present claim 1 (and hence, claims 3, 7, 8, 12, 75 and 76 that depend ultimately therefrom and that are also rejected) recites a nucleic acid-cationic immunoliposome complex comprising i) a cationic liposome, ii) an scFv antibody fragment, and iii) a nucleic acid wherein said nucleic acid-cationic immunoliposome complex is prepared by a method comprising: a) preparing the antibody fragment; b) directly conjugating the antibody

fragment to the cationic liposome to form a cationic immunoliposome, wherein the conjugation occurs via a sulfur atom which was part of a sulfhydryl group at a carboxy terminus on the antibody fragment prior to the conjugation; and c) mixing the cationic immunoliposome with the nucleic acid to form the nucleic acid-cationic immunoliposome complex; wherein the antibody fragment and the cationic liposome are present at a protein:lipid ratio (w:w) in the range of 1:10 to 1:40 and wherein the nucleic acid and the cationic liposome are present at a nucleic acid:lipid (μg:nmol) ratio in the range of 1:6 to 1:20. Present claim 73 recites a nucleic acid-cationic immunoliposome complex comprising i) a cationic liposome, ii) an scFv antibody fragment and iii) a nucleic acid, wherein the antibody fragment is directly conjugated to the liposome via a sulfur atom which was part of a sulfhydryl group at a carboxy terminus on the antibody fragment prior to the formation of the immunoliposome complex.

Applicants respectfully submit that while Chang may mention that ligands or antibodies can be covalently attached to cationic liposomes, Chang does not provide an enabling disclosure of such conjugation, including the required conjugating agents, reaction conditions, ratios of ligand and liposome, etc. In fact, the Example referred to by the Examiner, Example 13 of Chang, is written as a prophetic example, and thus represents at most a desired delivery method, but does not actually enable such a method. As discussed in detail below, while an inoperative reference may be cited by the Examiner under 35 U.S.C. § 103(a) for that which it does disclose (*see* M.P.E.P. § 2121.01(II)), Applicants submit that the direct conjugation of scFVs to cationic liposomes has not been enabled by any reference cited by the Examiner. Furthermore, as the Examiner notes, Chang does not disclose the direct conjugation of an antibody fragment to cationic liposomes, or the use of

the protein:lipid ratio of present claim 1. Thus, Chang is a seriously deficient reference on which to base a *prima facie* case of obviousness. Applicants respectfully submit that none of the references cited by the Examiner, alone or all in combination, cure the deficiencies in Chang.

As discussed in Applicants' Reply to Office Action filed on May 7, 2007, the disclosure of which is incorporated by reference herein in its entirety, Applicants respectfully submit that Yu does not disclose an antibody-fragment-targeted cationic immunoliposome complex, wherein the antibody fragment is directly conjugated to the cationic liposome, or the use of a sulfur atom which was part of a sulfhydryl group for such conjugation. In fact, Yu does not disclose an antibody fragment-targeted immunoliposome, or any method for preparing such a liposome (including mixing an antibody prior to or after mixing with DNA). Yu simply mentions in passing that liposomes could be targeted to the HER-2/neu-encoded p185 receptor. Yu provides no disclosure of the methods, ratios of lipid to protein, conditions, or other requirements for creating such immunoliposomes. Furthermore, Yu clearly does not disclose or enable any method for preparing such immunoliposomes, much less the immunoliposomes of the presently claimed invention. Yu also does not enable the direct conjugation of ligands or antibodies to cationic liposomes, and therefore does not cure the deficiencies noted in Chang.

On page 6 of the Office Action, the Examiner contends that Applicants have mischaracterized Yu. Applicants strongly disagree with the Examiner's contentions. As discussed above, while Yu does indeed mention that liposomes could be targeted to the HER-2/neu-encoded p185 receptor, as stated by the Examiner, "the ligand for the HER-2/neu-encoded p185 receptor was not available." Office Action at page 6, lines 7-8.

Applicants respectfully submit, therefore, while Yu may have suggested such targeted liposomes could be prepared, clearly Yu itself provides no disclosure of the methods, ratios of lipid to protein, conditions, or other requirements for creating such immunoliposomes, and therefore does not enable the production of such liposomes.

The Examiner contends that Marks discloses coupling of anti-ErbB2 svFvs to liposomes to prepare immunoliposomes containing chemotherapeutics. Applicants submit that while Marks mentions that scFv molecules were coupled to liposomes, there is no indication in Marks as to whether the scFvs were directly conjugated to the liposome, or attached via a poly(ethylene glycol) or other linker molecule. Furthermore, as discussed in Applicants' May 7, 2007 Reply, Marks does not disclose whether the liposomes that are being utilized are cationic or neutral liposomes. However, the reference cited at page 18, paragraph 206 of Marks, Kirpotin *et al.*, *Biochemistry 36*:66-75 (1997), indicates that the lipids used in Marks were palmitoyloleoylphosphatidylcholine (POPC), a neutral lipid as opposed to the cationic lipids recited in the present claims. Thus, Applicants submit that Marks and Yu do not cure the deficiencies noted above in Chang, as none of these references enable the direct conjugation of an scFV to a cationic liposome via a sulfur atom which was part of a sulfhydryl group at a carboxy terminus on the antibody fragment, and therefore, none of these references in combination render obvious the presently claimed invention.

With regard to the Examiner's reliance on Albritton to cure the deficiencies noted above, Applicants respectfully submit that this reference does not disclose the direct conjugation of antibody fragments to a cationic liposome through the use of a sulfur atom which was part of a sulfhydryl group at a carboxy terminus on the antibody fragment as required by the present claims. Applicants note that Example 13 of Albritton describes the

conjugation of the cationic liposomes to the mutant retroviral envelope proteins via an MPB-PE group on the liposome. There is no *direct conjugation* between the cationic liposome and an antibody fragment. While the disclosure cited by the Examiner at column 21, lines 2-13 of Albritton may disclose that single chain antibody fragments (scFVs) can be fused to the retroviral envelope proteins, there is no disclosure of *direct conjugation* between the liposome and the scFVs.

> Once the mutant envelope proteins and the genes encoding them are created, additional engineering of the retrovirus vector can occur. . . . The types of polypeptide molecules which *may be fused to the retroviral envelope protein* include immunoglobulin molecules or their fragments (e.g., scFV) . . . .

Albritton at column 20, line 64 through column 21, line 5 (emphasis added). Thus, contrary to the Examiner's assertion, Albritton does not disclose direct conjugation between the antibody fragment and the cationic liposome, where the conjugation occurs via a sulfur atom which was part of a sulfhydryl group at a carboxy terminus on the antibody fragment. At most, Albritton may disclose conjugation of a retroviral envelope protein (which may have a scFV fused to it) to a cationic liposome (*see* Albritton at column 49, lines 60-61, "liposomes . . . conjugated to mutant retroviral envelope proteins"), but there is clearly no disclosure in this reference of the *direct conjugation* of an scFV to a liposome via a sulfur atom which was part of a sulfhydryl group at a carboxy terminus of the scFV, as required in the presently claimed invention. Thus, Albritton does not cure the deficiencies noted above, even when used in combination with Chang, Yu and Marks, as these references collectively do not render obvious the presently claimed invention.

As discussed in Applicants' Reply to Office Action filed on May 7, 2007, cationic liposomes, such as those utilized in the presently claimed invention (and in Chang, Albritton

and Yu) have very different properties and characteristics that do not directly correlate with those of neutral liposomes. Marks does not provide a specific disclosure with regard to the methods by which the scFvs are coupled to the vesicles, simply that a free cysteine residue was added to the scFv. In addition, Marks does not disclose the use of cationic liposomes. One of ordinary skill in the art practicing the methods of Chang, Albritton or Yu would not have combined these disclosure with that of Marks, as the differences between the properties and characteristics of neutral liposomes (the subject matter of Marks) and cationic liposomes (the subject matter of Chang, Albritton and Yu, and the presently claimed invention) are so great, that combining these references would not have yielded predictable results, and in fact, a person of ordinary skill in the art at the time of filing of the present invention would have been directed away from making such a combination. *See, KSR Int'l. Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007) ("a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.").

Applicants respectfully submit that combining the disclosures of Chang, Albritton or Yu with the disclosure of Marks and the disclosures of Wright and Morishige, in order to attempt to produce the presently claimed invention, would not have been a predictable use of these references. As noted above, Chang, Albritton and Yu are directed toward the use of cationic liposomes to which nucleic acids are added in order to produce gene-transfer agents. The positive charge on the surface of the liposomes allows for an electrostatic interaction between the liposomes and the negatively charged DNA. Based on the statement in Yu that "one of our next efforts should be designing liposomes that can target the E1A gene to tumors," the Examiner contends that one of ordinary skill in the art would have sought to utilize the methods disclosed in Marks, Wright and Morishige to target these liposomes, and

hence, the presently claimed invention is rendered obvious. Applicants respectfully submit, as detailed in Applicants' Reply of May 7, 2007, that several years after the disclosure of Yu (and approximately one year prior to Applicants' filing of 35 U.S.C. § 120 priority application, PCT/US00/0432), persons of ordinary skill in the art were still struggling with how to target cationic liposomes. Furthermore, those who were working to solve the problem clearly would not have looked to disclosures utilizing noncationic liposomes.

Specifically, as detailed in Applicants' Reply of May 7, 2007, several years after the publication of Yu, scientists in the field of cationic liposome-based gene delivery (specifically one of the *same* scientists who identified "the next effort" in Yu, *see* Li and Huang, "Functional Pleomorphism of Liposomal Gene Delivery Vectors, Lipoplex and Lipopolyplex," *Liposomes. Rational Design*, Ed. A.S. Janoff, Marcel Dekker, Inc., New York, 1999, Chapter 4, pp. 89-124, submitted with May 7, 2007 reply) were still searching for methods to specifically target these carriers, and were primarily relying on the intrinsic, non-specific interactions between the liposomes and the target tissue. Applicants respectfully submit that this clearly demonstrates that the long felt need discussed in Yu was still an unsolved need several years later, despite the presence of the references cited by the Examiner that allegedly disclosed targeting *noncationic* liposomes (i.e., Wright and Morishige). As noted in *Graham*, "[s]econdary considerations such as commercial success, *long felt by unsolved need*, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." 35 U.S. at 17-18 (emphasis added).

> Li and Huang also state the following:
>
> Development of long-circulating lipid vectors, together with the use of a targeting ligand *might* provide a solution to the problem. It should be noted, however, that DNA is a large molecule with large hydrodynamic diameter as compared with chemotherapeutic drugs.

Li and Huang at page 120, lines 1-7 (emphasis added). Applicants respectfully submit that this not only demonstrates that targeting of DNA-liposome vectors was clearly unsolved, but also that one of ordinary skill in the art would not have predicted that antibody or antibody fragments could be directly conjugated to cationic liposomes (*i.e.*, the cationic liposomes of Chang, Albritton or Yu). Applicants respectfully submit that, in fact, Li and Huang actually teach *away* from directly conjugating antibody fragments (or antibodies) to liposomes comprising DNA on their surfaces. As stated in Li and Huang, "DNA is a large molecule with large hydrodynamic diameter as compared with chemotherapeutic drugs." One of ordinary skill in the art would not have predicted that additional molecules, such as antibodies or antibody fragments, could then *further* be added to these liposomes. The presence of large hydrodynamic diameter molecules on the surface of a cationic liposome, such as that disclosed in Yu, would have led one of ordinary skill in the art *away* from disclosures where antibodies or antibody fragments are directly conjugated to liposomes, such as noncationic liposomes that *do not* comprise DNA on their surface but rather encapsulate drugs or other agents (as disclosed in Marks, Wright and Morishige).

Thus, the disclosure of Li and Huang actually shows that the combination of Chang, Albritton or Yu with any of the disclosures of Marks, Wright or Morishige, to produce a targeted cationic nucleic acid-comprising liposome, would have been contrary to the knowledge of one of ordinary skill in the art. As set forth in M.P.E.P. § 2145(X)(D)(3),

proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *See also In re Hedges*, 783 F.2d 1038 (Fed. Cir. 1986) (Applicant's claimed process for sulfonating diphenyl sulfone at a temperature above 127°C was contrary to accepted wisdom because the prior art as a whole suggested using lower temperatures for optimum results as evidenced by charring, decomposition, or reduced yields at higher temperatures.). Furthermore, one of ordinary skill in the art would not have predicted that cationic liposomes could be targeted by directly conjugating an antibody fragment to the liposome, as recited in the presently claimed invention. Hence, the presently claimed invention represents more than the predictable use of the references cited by the Examiner. *See KSR*, 127 S.Ct. at 1740. Thus, one of ordinary skill in the art would not have predicted that the methods of targeting *noncationic* liposomes, as disclosed in Marks, Wright, or Morishige, could have been utilized with the DNA-comprising *cationic* lipids of Chang, Albritton or Yu.

In response to Applicants' rebuttal arguments of non-obviousness, the Examiner contends that Chang allegedly discloses the covalent attachment of ligands or antibodies to the surface of cationic liposomes that also further comprise a desired DNA. As noted above, Applicants respectfully submit that while Chang may indicate that antibodies can be conjugated to the surface of cationic liposomes, this reference does not provide any enabling disclosure of methods to perform such direct conjugation, rather only prophetic examples of such liposome compositions. Furthermore, as discussed in detail above, the disclosure of Albritton, while allegedly disclosing direct conjugation between a cationic liposome and an scFV, in fact simply discloses the conjugation of a targeted mutant envelope protein, not an scFV, to a cationic liposome. The Examiner has provided no disclosure that enables the direct conjugation of single chain antibody fragments to cationic liposomes. As discussed

above, a reference cited by an Examiner need not be enabling to be raised under 35 U.S.C. § 103(a) (*see* M.P.E.P. § 2121.01(II)). However, Applicants submit that, as set forth above, the direct conjugation of scFVs to cationic liposomes was not enabled by any knowledge available in the art, let alone any of the references cited by the Examiner. The disclosure of Chang thus is being utilized by the Examiner as allegedly disclosing direct conjugation of antibody fragments to cationic liposomes. The inoperability of Chang renders this reference insufficient on which to base a *prima facie* case of obviousness, absent disclosures or knowledge available the art, that would enable it. Applicants respectfully submit that the Examiner has not provided this required disclosure to enable Chang.

The Examiner also contends that one of ordinary skill in the art would have utilized the ratios of Fab' to liposome disclosed in Morishige when preparing liposomes comprising scFvs. Applicants respectfully submit that Morishige is limited to the use of Fab' fragments, and makes no mention of the use of scFvs. Fab' fragments are much larger molecules that scFvs, and hence, there is no reason to believe that the same ratios could be utilized in the preparation of scFv-comprising immunoliposomes. Applicants respectfully disagree with the Examiner's assertion, and submit that simply because one of ordinary skill in the art may have been aware of the molecular weight of both Fab' fragments and scFV, there is no reason to believe that one would have considered using the disclosed ratios of Fab' fragments in Morishige when working with scFV molecules. Furthermore, Applicants respectfully submit that the alleged disclosure of a ratio of 1:7.5 (antibody fragment:liposome) in Morishige does not render obvious the ratio of 1:10 to 1:40 (antibody fragment:liposome) set forth in present claim 1. Morishige discloses a very specific ratio of Fab' to liposome. There is no reason for a person of ordinary skill in the art to utilize this ratio for scFv molecules,

and certainly no predictable reason to modify the ratio significantly, as would be required to fall within the antibody:liposome ratio range of the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully submit that the Examiner has not provided sufficient evidence that the presently claimed invention has been rendered obvious by the disclosures of Chang, Yu, Marks, Albritton, Wright or Morishige, alone or in combination. Applicants submit that the differences between the presently claimed invention and the cited references are so great that one of ordinary skill in the art would not have predicted that the required elements could be combined to generate the presently claimed invention. *See KSR*, 1727 S.Ct. at 1740. Furthermore Applicants have submitted evidence in their previously filed Reply of a long felt but unmet need in the art (*see Graham*, 383 at 17), as well as disclosure that the required combination would have proceeded contrary to accepted wisdom in the art (*see Hedges*, 783 F.2d 1038). Hence, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 3, 7, 8, 12, 73, 75 and 76 under 35 U.S.C. § 103(a).

The Rejection Under 35 U.S.C. § 103(a) Over Chang in view of Yu, Marks, Albritton Wright and Morishige, and further in view of Xu and Scherman

In the Office Action at pages 7-8, section 6, the Examiner has rejected claims 2, 4 and 69 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Chang in view of Yu; Marks; Albritton; Wright; and Morishige; and further in view of Xu *et al.*, *Human Gene Therapy* *8*:467-475 (1997) (hereinafter "Xu"); and Scherman *et al.*, U.S. Patent No. 6,200,956 (hereinafter "Scherman"). Applicants respectfully traverse this rejection.

As discussed above, the Examiner asserts that Chang, Yu, Marks, Albritton, Wright and Morishige disclose the presently claimed invention, with the exception of an antibody fragment that is capable of binding to a transferrin receptor and a nucleic acid that encodes a wild type p53. The Examiner relies on the disclosures of Xu and Scherman to cure these deficiencies.

With regard to Xu, the Examiner asserts that Xu discloses the use of transferrin-cationic liposomes for delivery of wild type p53 to various tumors. The Examiner also contends that Scherman discloses immunoliposomes, including cationic lipids, comprising single chain transferrin antibody fragments as targeting molecules for cells such as tumor cells.

The Examiner concludes that it would have been obvious for one of ordinary skill in the art to combine these various disclosures to have made the immunoliposomes of the presently claimed invention for delivery of a p53 gene, using a scFv antibody fragment with a specificity for transferrin coupled directly to the liposome, based upon the various disclosures of Chang, Yu, Marks, Albritton, Wright, Morishige, Xu and Scherman. Applicants respectfully disagree with the Examiner's conclusion and the contentions on which they are based.

Applicants note that the Examiner stated that Xu and Scherman were being argued separately in the Reply dated May 7, 2007. Applicants respectfully disagree with this characterization and submit that Xu and Scherman were discussed in the context of the entire rejection raised by the Examiner. The discussion of the two references in order was only provided for clarity purposes.

Applicants respectfully submit that the ordinarily skilled artisan would not have predicted that any of the cited references could have been utilized in combination with Chang, Albritton or Yu, let alone to produce the presently claimed invention. As discussed hereinabove, one of ordinary skill in the art would not have predicted that methods for targeting noncationic, non-nucleic acid-comprising liposomes could be used to target cationic liposomes. In fact, such a combination would have proceeded contrary to the excepted wisdom in the art at the time. Neither the disclosure of Xu, nor the disclosure of Sherman, are able to cure the deficiencies in these references discussed in the preceding section of this Reply, which are reiterated and incorporated by reference herein.

Specifically, Xu does not disclose the use of scFv fragments, disclosing instead liposomes complexed with transferrin, as a targeting ligand. Transferrin, and an scFv antibody fragment, such as the anti-transferrin receptor scFv used in examples of the present application, are very different molecules, with different sizes and very different functions. One of ordinary skill in the art would not have predicted that one could be substituted for the other. Thus, whether or not Xu discloses transferrin-targeted liposomes and/or the use of DNA encoding wild-type p53, this reference does not cure the various deficiencies noted above and thus, even in combination with any of the other references, does not render obvious the presently claimed invention.

With regard to Scherman, the Examiner asserts that throughout page 8, Scherman discloses using scFV antibody fragments linked to cationic lipids. However, a search of Scherman for disclosure of either the terms "scFV" or "single chain antibody" revealed that neither of these terms is even mentioned in the specification. Thus, Scherman does not disclose conjugation of scFv fragments to liposomes as stated by the Examiner.

Furthermore, the reference does not disclose direct conjugation, including conjugation via a sulfhydryl group, nor what ratios of protein and lipid would be required to prepare the cationic immunoliposomes of the present invention. Therefore, Scherman does not cure the deficiencies noted above in the various references, and even in combination, the cited references do not and cannot render obvious the presently claimed invention.

Furthermore, Xu and Scherman do not enable the direct conjugation of an antibody fragment to a cationic liposome to form a cationic immunoliposome, wherein the conjugation occurs via a sulfur atom which was part of a sulfhydryl group at a carboxy terminus on the antibody fragment. Therefore, these references, even in combination with Chang, Yu, Marks, Albritton, Wright and Morishige, do not render obvious the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully submit that claims 2, 4 and 69 are not rendered obvious by the disclosures of Chang in view of Yu, Albritton, Marks, Wright, Morishige, Xu and Scherman, alone, or in combination. Hence, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are respectfully requested.

Conclusion

All of the stated grounds of rejection have been properly traversed, rendered moot or otherwise overcome. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn.

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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